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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32723A/USN	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11379	International filing date *(day/month/year)* 14.10.2003	Priority date *(day/month/year)* 15.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/663		
Applicant NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.04.2004	17.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Trifilieff-Riolo, S Telephone No. +49 89 2399-7514

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11379

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1, 5-11, 15-18 (IA)

   because:

   ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18 (see sep. sheet)
	No:	Claims	

2. Citations and explanations

   see separate sheet

D1: LEVY R J ET AL: "Polymeric drug delivery systems for treatment of cardiovascular calcification, arrhythmias and restenosis" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 36, no. 1, 1 September 1995 (1995-09-01), pages 137-147, XP004037475 ISSN: 0168-3659
D2: WO 01/49295 A (UNIV CALIFORNIA) 12 July 2001 (2001-07-12)
D3: JAGDEV S P ET AL: "THE BISPHOSPHONATE, ZOLEDRONIC ACID, INDUCES APOPTOSIS OF BREAST CANCER CELLS: EVIDENCE FOR SYNERGY WITH PACLITAXEL" BRITISH JOURNAL OF CANCER, LONDON, GB, vol. 8, no. 84, 2001, pages 1126-1134, XP008001603 ISSN: 0007-0920
D4: WO 00/03677 A (HADASIT MED RES SERVICE ;YISSUM RES DEV CO (IL); DANEBERG HAIM (IL) 27 January 2000 (2000-01-27)
D5: YLITALO RITVA ET AL: "Suppression of immunoreactive macrophages in atheromatous lesions of rabbits by clodronate" PHARMACOLOGY AND TOXICOLOGY, vol. 90, no. 3, March 2002 (2002-03), pages 139-143, XP002268659 ISSN: 0901-9928
D6: KOSHIYAMA HIROYUKI ET AL: "Decrease in carotid intima-media thickness after 1-year therapy with etidronate for osteopenia associated with type 2 diabetes" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 85, no. 8, August 2000 (2000-08), XP002268658 ISSN: 0021-972X
D7: PRICE ET AL.: "bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption" ARTERIOSCLEROSIS, THROMBOSIS AND VASCULAR BIOLOGY, vol. 21, no. 5, 2001, XP002268657
D8: YLITALO: "Bisphosphonates and atherosclerosis" GENERAL PHARMACOLOGY, vol. 35, 2002, pages 287-296, XP002268656

Section III:
Claims 1, 5 to 11, 15 to 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Section V:

1. D1 describes the use of bisphosphonates (particularly of etidronate= EHDP) possibly synergistically combined with metal salts to inhibit aortic wall calcification (p. 140, right-

hand col., 1st paragraph). These compounds are administered locally as controlled release implants.
Thus the subject-matter of claim 4, 5, 7, 8, 9, 10, 11, 12-16 is not novel

D2 describes the use of bisphosphonates among which zoledronate (p. 16, l. 1-12) to treat atherosclerosis and non-atheromatous arterioscleroses (p. 15, l. 1-17). The subject-matter of claims 1-8 and 16-18 is not novel.

D3 describes the use of zoledronate to induce apoptosis of breast cancer cells. Thus subject-matter of claims 7, 16, 17 and 18 is not novel.

D4 (p. 6, l. 12-18 and p. 7, l. 17-30) describes the use of bisphosphonates (e.g. clodronate, etidronate, tiludronate), possibly combined with pyrophosphates, to treat vascular restenosis. The administration can be local by means of a stent.
The subject-matter of claims 7, 8-11, 15, 16 is not novel.

Lack of novelty is emphasized by the following documents:
D5 which describes that clodronate injected intravenously to rabbits has an antiatherosclerotic effect.
D6 which describes the antiatherogenic effect of etidronate.
D7 which describes that alendronate and ibandronate inhibit artery calcification.
D8 which describes the antiatherogenic effect of several bisphosphonates.

2. The requirements for clarity (A. 6) are not met for the following claims:
claims 5 and 6: they are independent claims but encompass different subject-matter (method or use)
claims 13 and 14: they are drafted as depending on claim 12, i.e. they should contain all the features of claim 12 including the mandatory presence of zoledronic acid as feature b) which is not the case (zoledronic acid is only cited as an example in these claims).

3. For the assessment of the present claims 1, 5 to 11, 15 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a

known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.